2. IGF-II is capable of promoting cartilage matrix maintenance in injury-induced OA in mice and in human OA cartilage ex vivo cultures.

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CHANGES IN PATELLOFEMORAL BONE MARROW LESIONS AND KNEE PAIN: NATURAL HISTORY AND THE ASSOCIATIONS WITH STRUCTURE

Z. Zhu †, C. Ding †, X. Jin †, B. Antony †, W. Han †, L. Laslett †, F. Cicuttini ‡, G. Jones †. † *Menzies Inst. for Med. Res., Hobart, Australia;* ‡ *Dept. of Epidemiology and Preventive Med., Monash Univ., Melbourne, Melbourne, Australia*

Purpose: Bone marrow lesions (BMls) are recognized as an important subchondral feature in knee OA and play a vital role in the diease progression. The patellofemoral joint (PFJ) is a common site of pain and contributes to functional limitations among OA patients. However, there are very few clinical or epidemiological studies that reveal the association between PFJ BMLs and clinical symptoms as well as cartilage structural morphologies. Meanwhile, the natural history of PFJ BMLs has not yet been described. The aims of this study were, therefore, to describe the natural history of MRI-detected BMLs in PFJ over 2.6 years and evaluate the association between increases in PFJ BMLs, knee pain and knee cartilage morphology in older adults.

Methods: 406 males and females were randomly selected from local community (mean age 63 years, range 51 to 79) and followed up for 2.6 years. PFJ BMLs were determined on T2-weighted fat saturated magnetic resonance imaging (MRI) using Whole-Organ MRI Score system (WORMS). Knee cartilage volume and cartilage defects scores (0-4) were determined on T1-weighted fat suppression MRI using WORMS. Knee pain was accessed by Western Ontario and McMaster Universities Osteoarthritis (WOMAC) scores. Student's t-tests and Pearson's χ^2 tests were used to compare the differences between subjects with and without an increase in PFJ BMLs. Crude and adjusted linear regression was used to determine whether PFJ BML changes over 2.5 years were associated with changes in knee pain in the different sub-scales over 5 years, before and after adjustment for potential confounders. Binary logistic regression was used to examine the associations between increases in PFJ BMLs as an outcome, and baseline cartilage volumes as well as baseline cartilage defect scores as predictors, both before and after adjustment for potential confounders.

Results: At baseline, 27% (n=109) had PFJ BMLs, 24% of these showed progression (change in score of ≥ 1) at follow-up, 44% persisted and 21% completely resolved. Of those 73% (n=297) who did not have PFJ BMLs at baseline, 19.7% of them developed new PFJ BMLs over 2.6 years. In multivariable analysis, change in PFJ BMLs was positively associated with increases in total knee pain (β: 0.81, 95% CI: 0.15, 1.48) and knee pain when going up/down stairs (β: 0.29, 95% CI: 0.08, 0.50) over 5 years. While baseline patellar cartilage volume predicted a decrease in PFJ BMLs (OR: 0.62, 95% CI: 0.43, 0.90), baseline patellar cartilage defects were associated with an increase in PFJ BMLs (OR: 1.75, 95% CI: 1.28, 2.40) over 2.6 years. Tibiofemoral cartilage volume and defects were not associated with changes in PFJ BMLs.

Conclusions: PFJ BMLs are not static and change is clinically relevant. An increase in PFJ BMLs can be predicted by reduced patellar cartilage volume and increased patellar cartilage defects site-specifically.

	Patellofemoral joint BMLs		
	No Increase (n=321)	Increase (n=85)	*p* value
Age	62.9±7.1	61.8±7.6	0.246
Females (%)	50	50	0.863
BMI (kg/m^2)	27.5±4.3	28.0±4.9	0.382
ROA present (%)	70	61	0.754
Knee pain (%)	50	40	0.541
Smoked (%)	50	40	**0.037**
Tibia Bone size (cm^2)	33.6±4.9	32.7±4.2	0.133
Patella BMLs at baseline (%)	18	19	0.873
Tibiofemoral BMLs at baseline (%)	32	42	0.086
Patella Cartilage defect score at baseline	1.5±0.9	1.9±1.0	**0.001**
Tibiofemoral Cartilage defect score at baseline	4.2±1.8	4.4±1.6	0.372
Patella cartilage volume at baseline (ml)	3.4±0.9	3.2±0.9	**0.031**
Tibia cartilage volume at baseline (ml)	5.1±1.2	5.0±1.0	0.291

Abbreviation: ROA, radiographic osteoarthritis; BMI, body mass index; BMLs, bone marrow lesions. *Data are given as mean ± SD unless otherwise indicated. Student's t-test or chi-square test (where appropriate) were used to test for significant differences between two groups. An increase in patellofemoral joint (PFJ) BMLs is defined as a change in BMLs of ≥1 from baseline to follow-up (vs. no increase).

	Univariable β (95% CI)	Multivariable * β (95% CI)	Multivariable** β (95% CI)
Total WOMAC knee pain	**0.78 (0.15, 1.40)**	**0.81(0.17, 1.45)**	**0.79 (0.11, 1.47)**
Pain walking on a flat surface	0.03 (-0.12, 0.18)	0.03 (-0.12, 0.19)	0.05 (-0.11,0.22)
Pain going up and down stairs	**0.28 (0.07, 0.48)**	**0.27 (0.07, 0.47)**	**0.29 (0.08, 0.50)**
Pain at night when in bed	**0.22 (0.03, 0.41)**	**0.22 (0.02, 0.42)**	0.19 (-0.02, 0.40)
Pain sitting or lying	0.12 (-0.02, 0.27)	0.13 (-0.02, 0.28)	0.11 (-0.05, 0.27)
Pain standing upright	0.13 (-0.02, 0.29)	0.15 (-0.01, 0.32)	0.15 (-0.01, 0.32)

*Adjusted for age, sex, BMI, ROA, NSAIDs use and smoking status, **further adjusted for baseline patellofemoral BML, baseline tibiofemoral BMLs, baseline patella cartilage defect and baseline tibiofemoral cartilage defect. Statistical significances are shown in bold.

	Univariable RR (95% CI)	Multivariable* RR (95% CI)	Multivariable** RR (95% CI)
Baseline patella cartilage volume (ml)	**0.78 (0.62, 0.99)**	**0.68 (0.50, 0.92)**	**0.69 (0.48, 0.98)**
Baseline Tibial cartilage volume (ml)	0.94 (0.83, 1.07)	0.86 (0.69, 1.07)	0.87 (0.70, 1.08)
Baseline patella cartilage defects (per grade)	**1.35 (1.13, 1.60)**	**1.50 (1.19, 1.90)**	**1.67 (1.26, 2.19)**
Baseline Tibiofemoral cartilage defects (per grade)	1.04 (0.96, 1.13)	1.03 (0.93, 1.14)	0.99 (0.89, 1.10)

*Adjusted for age, sex, BMI, baseline patella BMLs, smoking status and ROA. ** further adjusted for baseline PFJ BMLs, baseline total tibiofemoral BMLs, total cartilage defects and total cartilage volume. Significant differences are shown in bold.

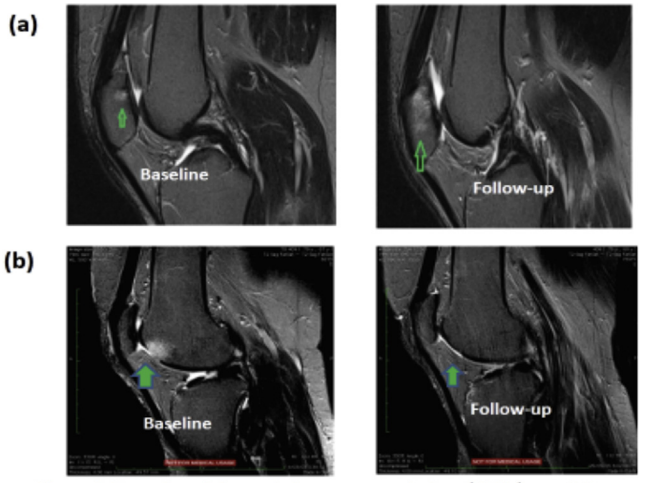

Figure 1 Examples of change in bone marrow lesions (BMLs) over 2.6 years.
(a) PFJ BMLs increase from baseline to follow-up.
(b) PFJ BMLs completely resolved from baseline to follow-up.